REMARKS

The foregoing amendments and the following remarks are submitted in response to the communication dated June 11, 2003.

Status of the Claims

Claims 1-32 are pending in the application. Claims 1-23, which are withdrawn from consideration have been canceled without prejudice. Claims 29 and 30 have been canceled without prejudice. Claims 24-28 and 31-32 have been amended and new Claims 33 and 34 are presented in order to more particularly point out and distinctly claim that which Applicants regard as the invention. Support for the amended claims and newly presented claims can be found generally through Applicants' specification. In particular, support for new claims 33 and 34 can be found at page 67, lines 12-16.

Priority

The Examiner correctly notes that the instant Application claims priority to two U.S. Applications, specifically U.S.S.N. 09/668,508 filed September 22, 2000 and U.S.S.N. 09/404,895 filed September 19, 1999, and requests that Applicants refer to the prior Applications in the first sentence of the Application. Applicants have above amended the Specification to properly reference the related priority Applications and submit that the instant Application now correctly meets this requirement.

Specification

The Examiner objects to the disclosure because of certain informalities. In particular, the Examiner notes that at pages 113 to 114 there is a large blank area and furthermore the sentences bridging pages 113 to 114 do not make sense. Applicants have reviewed the Specification and it appears that a printing or xeroxing error may have occurred such that certain of the text was not copied or printed in the Patent Office's copy of the instant Application. Applicants have above amended the Specification to insert the text which was inadvertently not xeroxed or printed. Applicants point out and assert that this text does not present or constitute new matter in as much as the text is identical to corresponding text in the priority Application U.S.S.N. 09/668,508 (the "'508

Application") filed September 22, 2000, and particularly precisely corresponds to the text in the'508 Application at page 106, lines 7 through 25.

In addition, the Examiner objects to the Specification in its recitation of "Abstract" , particularly in that the term is recited at pages 234, 255 and 274 and this is confusing. Applicants have above amended the Specification to remove the term "Abstract" at pages 234, 255 and 274, so that the term appears only once, at the final page of the Specification.

Applicants submit that the Examiner's objections to the Specification have been addressed and request acceptance of the Specification as now amended.

The Specification Fully Enables the Claimed Invention

The Examiner has rejected Claims 24-32 under 35 U.S.C. 112, first paragraph, because the Specification fails to comply with the enablement requirement. Specifically, the Examiner states that "in view of the quantity of experimentation necessary to overcome the unpredictabilities associated with stem cell transplantation and gene therapy, the lack of direction or guidance provided by the specification to carry out stem cell therapy, as broadly claimed, for the treatment of any disease, the lack of direction or guidance provided by the specification to carry out gene therapy utilizing transfected stem cells, for the treatment of any disease, involving any particular vector, promoter, route of administration and subject, the breadth of the claims directed to any particular vector, promoter, route of administration or subject, as well as the unpredictable and undeveloped state of the art of stem cell transplantation and gene therapy it would have required undue experimentation for one of skill in the art to make and/or use the claimed invention". Applicants respectfully disagree and submit that the Specification provides guidance and examples that, combined with the significant knowledge and skill of the skilled artisan, and importantly considering the novel and remarkable capabilities and characteristics of the pluripotent embryonic-like stem cells of the instant invention, enable the practice of the invention, and in particular enable the use of the stem cells of the invention in methods of transplantation, treatment and gene therapy, without undue experimentation.

Applicants point out that the Specification provides direction or guidance and specific examples suitable for the skilled artisan to carry out pluripotent embryonic-like stem cell therapy and to carry out gene therapy utilizing transfected pluripotent embryonic-

like stem cells. The Specification details the isolation and characterization of embryonic-like stem cells from various non-embryonic and postnatal sources and the differentiation of these novel stem cells to various cell types of each of ectodermal, endodermal and mesodermal origin, both *in vitro* and *in vivo* in animal models. At pages 6-9 of the Office Action, the Examiner appropriately points to teaching in the Specification by way of particular Examples of differentiation of the pluripotent embryonic-like stem cells into various cell types both in *in vitro* studies and in *in vivo* models. Similarly, Applicants point out that the Specification, in addition to demonstrating differentiation into many different cell types of each of the endodermal, ectodermal and mesodermal lineages *in vitro*, details the introduction of the claimed stem cells into animals *in vivo* and the proliferation and differentiation of these stem cells into appropriate, even functional, cells, including as follows: lacZ-transfected rat stem cells in outbred rats (Example 12), human stem cells in mice in bone marrow (Example 15), lacZ-transfected and isolated rat stem cells in a rat hindlimb ischemia model (Examples 18 and 19), rat lacZ-transfected stem cells in cardiac repair in a myocardial infarction rat (Example 21), rat stem cells trasnplanted into the striatum of adult rats and showing neurological expression (Example 22 and 23), rabbit stem cells in an osteochondral defect in rabbits (Example 26), and rat stem cells in a spinal cord injury site (Example 27).

The skilled artisan is thus provided extensive evidence and guidance for generating cells or tissues of various origins and types by the teaching and evidence in the Specification, including the above detailed examples. Applicants further submit that it is unnecessary to provide working examples of all cell and/or tissue types and all therapies or defects so long as there is a sufficient and enabling disclosure to guide the skilled artisan. In addition to the teaching of the Specification and the significant knowledge of the skilled artisan, the prior art provides teaching and methods for the differentiation and characterization of cells and tissues from ectodermal, endodermal and mesodermal stem cells, which teaching is clearly applicable to the embryonic-like stem cells as they are precursors of these more restricted and further differentiated stem cells. As is evidenced, for instance, by the examples of the Specification, the culture of the embryonic-like stem cells under conditions appropriate for mesenchymal stem cells results in differentiation of the cells of the invention to various mesenchymal derived cells.

The Examiner cites various references which he asserts demonstrate the unpredictability of the claimed methods. Applicants point out that these references relate to various stem cells, including ES cells, each of which are absolutely distinct from the pluripotent embryonic-like stem cells of the instant invention. In particular, none of the cells which are the subject of or are criticized in the references for their limitations or obstacles have the characteristics of the stem cells of the present invention, which are important and critical to the application and more predictable use of the instant stem cells in the claimed methods. In particular, the pluripotent embryonic-like stem cells of the present invention are isolated from non-embryonic or postnatal sources (even adult sources), therefore the need for stem cells that will probably be derived from allogeneic sources, as criticized in Strom *et al.*[Curr Opin Immunol 14(5):601-605, October 2002] for instance, or for which screening of donor cells is an obstacle, as criticized in Henningson *et al.*[J Allergy Clin Immunol 111(2):S745-S753, 2003] and in Prelle *et al.*[Anat Histol Embryol 31(3):169-186, June 2002] for instance, may be avoided because the instant stem cells may be obtained even from an adult as an autologous source. In addition, the stem cells of the present invention have been demonstrated to transplant and integrate even in an unrelated host in the absence of a host immune response. The Examiner cites Strom *et al.* as indicating overcoming immune rejection as an important factor in unpredictability and, at page 12 of the Office Action, the Examiner asserts that the Specification fails to show transplantation of the claimed stem cells would not cause rejection. In fact, the Specification demonstrates the making and using of a therapeutically effective amount of pluripotent embryonic-like stem cells and transplantation and integration of the cells to tissue in the absence of a host immune response. Applicants point out that in Example 12, pages 249-250, rat pluripotent embryonic-like stem cells, when implanted into outbred (ie; genetically and immunologically unmatched) rats, do not induce graft versus host disease, thus successfully avoiding the host's immune system. In Example 15 at pages 244-246, it is demonstrated that human pluripotent embryonic-like stem cells can be co-transplanted with mouse pluripotent embryonic-like stem cells into mice and shown to populate the bone marrow of the transplanted mice. Similarly, in Example 18 at pages 263-264, genomically labeled β-gal rat pluripotent embryonic-like stem cells were administered and tested *in vivo* in a hindlimb ischemic model in

rats. Post transplant, labeled rat cells were incorporated into the hindlimb at the ischemic site when administered intramuscularly or intravenously, and in addition, on intravenous injection, labeled cells were observed in the bone marrow. Graft versus host disease or immunological rejection were not observed in these *in vivo* studies. Thus, the Specification demonstrates that the unique pluripotent embryonic-like stem cells of the present invention can be transplanted to obtain appropriate integration at a desired site and can successfully avoid the host's immune system.

Applicants acknowledge that, while some experimentation to use such embryonic-like stem cells in the claimed methods would be necessary, such experimentation would utilize well known and standard skills and would not constitute undue experimentation. With regard to the determination of what is undue experimentation, the PTO and the courts have commented that "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." MPEP § 2164.01, *citing M.I.T. v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). The test of enablement is not whether experimentation is necessary, but whether or not it is undue. *Ibid, citing In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). Factors to consider in determining undue experimentation include (1) the quantity (time and expense) of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; (8) and the breadth of the claims. *Ibid, citing In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In the present instance: (1) the quantity of experimentation, while significant, is not undue for the skilled artisan in these particular methods; (2) the direction or guidance provided by the specification is sufficient for the skilled artisan and appropriate for the time; (3) a number of working examples are provided; (4) the nature of the invention, including, but not limited to the disclosure of the differentiation of these stem cells to cells of any of endodermal, ectodermal and mesodermal origin *in vitro* and *in vivo* and the transduction and expression of genes in these cells *in vitro* and *in vivo*; (5) the extent of prior art available to those skilled in the art with regard to the use of stem cells and the practice of the methods was significant at

the time of filing; (6) the relative skill of those in the art is substantial - the level of skill in the art corresponds to that of a Ph.D. with postdoctoral experience or an M.D.; (7) the disclosure and teaching of differentiation of embryonic-like stem cells into cells and tissues of various origins and types both *in vitro* and *in vivo*; and (8) the breadth of the claims is commensurate with the significant skill of those in the art and the significant applicability of the stem cells of the invention to use in various methods.

In view of the foregoing, Applicants submit that given the guidance provided by the Specification and the significant level of skill in the art, a person of ordinary skill could make a therapeutically effective amount of the pluripotent embryonic-like stem cells and use them in the claimed methods of the present invention. In view of the foregoing remarks, Applicants submit that the Examiner's rejection under 35 U.S.C. 112, first paragraph, may properly be withdrawn.

Particularity and Distinctiveness of the Claims

The Examiner has rejected Claims 24-32 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter applicant regards as the invention. The Examiner remarks that the claims are unclear in the recitation of "embryonic-like" stem cells, indicating that, while the Specification states that these cells are derived from non-embryonic or postnatal animal cells or tissues, it is unclear how these cells would be embryonic-like. Applicants respectfully disagree and submit that the term "embryonic-like" stem cell is clear to the skilled artisan, given the teachings and description set out in the Specification. The Specification, including at page 41, lines 20-23, particularly and distinctly sets out the description and definition of embryonic-like stem cell in stating that it extends to

> those cell(s) and/or cultures, clones, or populations of such cell(s) which are derived from non-embryonic or postnatal animal cells or tissue, are capable of self regeneration and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages.

The above definition sets the embryonic-like pluripotent stem cells of the present invention - or

any shortened terminology used to refer to the cells of the present invention, including embryonic-like stem cells and stem cells (particularly wherein no additional characteristic or term precedes the word stem cell) - apart and distinct from other previously identified and described stem cells of various types, derivation and nature. For instance, the Specification, including at page 2, lines 20-31, at page 4, line 25 to page 5, line 6, and at pages 42-44, describes and defines various particular and distinct types of characterized stem cells, including unipotent stem cells, bipotent stem cells, pluripotent endodermal stem cells, pluripotent mesenchymal stem cells, and pluripotent ectodermal stem cells. Each of these particular stem cells, which are distinct in and of themselves from the stem cells (embryonic-like pluripotent stem cells) of the present invention, have a particular lineage capacity and/or commitment. Remarkably, as described and demonstrated in the Specification, the embryonic-like pluripotent stem cells of the present invention are lineage-uncommitted and have the capacity to self-renew and to differentiate to cells of any of the endodermal, ectodermal, and mesodermal lineages. To the extent that they have the capacity to differentiate to cells of any lineage (endodermal, ectodermal or mesodermal), they are thus embryonic-like, in as much as it is well recognized that the embryo and its initial cells differentiate into all the cells of the body (which are of endodermal, ectodermal or mesodermal lineage origin). Applicants' "embryonic-like" pluripotent stem cells are distinct from embryonic stem cells or ES cells, however, as described and claimed, including in that they are isolated from non-embryonic or postnatal cells or tissue. Applicants submit that the recitation embryonic-like pluripotent stem cell particularly points out and may be used to distinctly claim the subject matter Applicants regard as the invention.

The Examiner rejects Claim 26 as incomplete because he asserts that at least the basic steps must be recited in a positive, active fashion. Applicants have above amended Claim 26 to address the Examiner's rejection.

The Examiner rejects Claims 27-30 as incomplete because he asserts that the claims require clear and defined steps. Applicants have above amended Claims 27 and 28 to address the Examiner's rejection. Applicants have above canceled Claims 29 and 30, making this rejection moot.

The Examiner further rejects Claims 27, 29 and 31 as vague in their recitation "and/or" as it is unclear if the information following the phrase is intended to further limit or expand the claim. Applicants have above amended Claims 27 and 29 to address the Examiner's rejection. Claim 30 has now been canceled, making its rejection moot.

In view of the foregoing amendments and remarks, Applicants submit that the Examiner's 112, second paragraph, rejections are obviated and should be withdrawn.

The §102 Rejections

The Examiner has rejected Claims 24-32 under 35 U.S.C.102(b) as being anticipated by Kiem *et al.* [Blood, 92(6):1878-1886, September 15,8] and asserts that Kiem *et al.* teach the claimed invention. Applicants respectfully disagree. Kiem *et al.* teach that baboon hematopoietic stem cells (HSC) were harvested after *in vivo* priming using stem cell factor and granulocyte colony-stimulating factor, the HSCs transfected with a vector carrying a gene encoding human placental alkaline phosphatase, and babboons then transplanted with the transduced cells and the blood and marrow analyzed for the presence of vector sequences. Anticipation is a question of fact. As defined by the Federal Circuit, "[t]o anticipate a claim a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject-matter." *PPG Industries, Inc. vs Guardian Industries Corp., 37 USPQ2d 1618 (Fed. Cir. 1996) (emphasis added).* Kiem *et al* neither discloses every element of the rejected claims nor enables one skilled in the art to make or practice the claimed inventions. Applicants agree and acknowledge that Kiem *et al.* teaches and confirms that a hematopoietic stem cell can be transfected with a gene vector in vitro, transplanted into an animal and the animal demonstrated to express the gene encoded by the vector in its blood or marrow *in vivo*. However, and importantly, while Kiem *et al.* teaches that gene therapy with a hematopoietic stem cell is possible, it does not teach or anticipate the methods claimed by applicant. Applicant claims methods of transplantation, administration, prevention and treatment utilizing the pluripotent embryonic-like stem cells of Applicants. The pluripotent embryonic-like stem cells of the present invention are absolutely and importantly distinct from the cells of Kiem *et al.* It is well recognized to the skilled artisan and described by Kiem *et*

al. that HSCs are hematopoietic repopulating cells, stem cells capable of differentiating into cells of a defined and specific lineage, particularly cells of the blood system or hematopoietic lineage. These HSCs cannot differentiate into any cell of the endodermal, ectodermal or mesodermal as is the novel characteristic of Applicants' pluripotent embryonic-like stem cells.

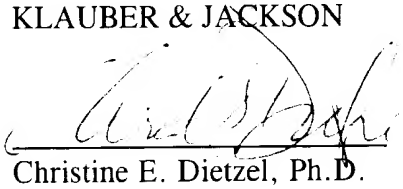
The Examiner has further rejected Claims 27-31 under 35 U.S.C.102(b) as being anticipated by Wang *et al.* [Transplantation, 65(2):188-192, January 1998] and asserts that Wang *et al.* anticipate the claimed invention. Wang *et al.* teach that rats were transfected with liver, pancreas, heart and kidney allografts and it was found that liver allografts were spontaneously accepted. The Examiner asserts that the allografts as taught by Wang would be considered cells or tissues derived from pluripotent embryonic-like stem cells. Applicants respectfully disagree and point out that anticipation is a question of fact. The pluripotent embryonic-like stem cells of the present invention are absolutely and importantly distinct from the allografts of Wang *et al.* Applicants further point out that, in view of the above Claim amendments, this rejection, which refers to cells or tissues derived from pluripotent embryonic-like stem cells is moot. Wang *et al* neither discloses every element of the rejected claims nor enables one skilled in the art to make or practice the anticipating subject matter.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks in the file history of the instant Application. The Claims as amended are believed to be in condition for allowance, and reconsideration and withdrawal of all of the outstanding rejections is therefore believed in order. Early and favorable action on the claims is earnestly solicited.

Respectfully submitted,

KLAUBER & JACKSON



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Complete Listing of Claims in Application U.S.S.N. 09/820,320

Claims 1-23 (Cancelled)

Claim 24 (currently amended): A method of transplanting pluripotent embryonic-like stem cells in a host comprising ~~the step of~~ introducing into the host pluripotent embryonic-like stem cells, derived from non-embryonic or postnatal animal cells or tissue, capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages, wherein the stem cells proliferate and differentiate in the host ~~the stem cells of Claim 1~~ .

Claim 25 (currently amended): A method of providing a host with purified pluripotent embryonic-like stem cells comprising ~~the step of~~ introducing into the host ~~the~~ pluripotent embryonic-like stem cells , derived from non-embryonic or postnatal animal cells or tissue, capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages, wherein the stem cells proliferate and differentiate in the host ~~of Claim 1~~.

Claim 26 (currently amended): A method of *in vivo* administration of a protein or gene of interest in a mammal comprising ~~the step of~~ transfecting a ~~the~~ pluripotent embryonic-like stem cell derived from non-embryonic or postnatal animal cells or tissue, capable of self-renewal and capable of differentiation to cells of endodermal, ectodermal and mesodermal lineages ~~of Claim 1~~ with a vector comprising DNA or RNA which expresses a protein or gene of interest, and administering the transfected pluripotent embryonic-like stem cell to said mammal, wherein the protein or gene of interest is expressed in said mammal.

Claim 27 (currently amended): A method of preventing or ~~and/or~~ treating cellular debilitations, derangements, ~~and/or~~ dysfunctions or ~~and/or~~ other disease states in mammals, comprising administering to a mammal a therapeutically effective amount of pluripotent embryonic-like stem cells wherein the administered stem cells proliferate and differentiate in said mammal to prevent or treat the cellular debilitation, derangement, dysfunction or other disease state in said

mammal ~~, or cells or tissues derived therefrom~~.

Claim 28 (currently amended): A method of tissue repair or transplantation in mammals, comprising administering to a mammal a therapeutically effective amount of pluripotent embryonic-like stem cells wherein the administered stem cells proliferate and differentiate to form the cells or tissue which is in need of repair or transplantation in said mammal ~~, or cells or tissues derived therefrom~~ .

Claim 29 (cancelled)

Claim 30 (cancelled)

Claim 31 (currently amended): A pharmaceutical composition for the treatment of cellular debilitation, derangement or ~~and/or~~ dysfunction in mammals, comprising:

A. a therapeutically effective amount of pluripotent embryonic-like stem cells~~, or cells or tissues derived therefrom~~; and

B. a pharmaceutically acceptable medium or carrier.

Claim 32 (currently amended): The pharmaceutical composition of Claim 31 ~~28~~ further comprising one or more ~~a~~ proliferation factor or lineage-commitment factor.

Claim 33 (new) : A method of treating cellular or tissue loss or deficiency in a mammal comprising administering to said mammal a therapeutically effective amount of pluripotent embryonic-like stem cells, wherein the administered stem cells proliferate and differentiate to form the cells or tissue which is lost or deficient in said mammal.

Claim 34 (new): The method of Claim 33 wherein the pluripotent embryonic-like stem cells are administered in combination with one or more proliferation factor or lineage commitment factor.